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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

EDWARD A. BOYSE et al.

Application No. 07/119,746

Filed: November 12, 1987

For: ISOLATION AND PRESERVATION OF FETAL AND NEONATAL HEMATOPOIETIC STEM AND PROGENITOR CELLS OF THE BLOOD

Attorney Docket No. 6287-003

Group Art Unit: 182

Examiner: Sam Rosen

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INFORMATION DISCLOSURE STATEMENT UNDER 37 C.F.R. § 1.56

Honorable Commissioner of Patents and Trademarks
Washington, D.C. 20231

S I R:

In accordance with the duty of disclosure imposed by 37 C.F.R. § 1.56, Applicants hereby direct the Examiner's attention to the following references, copies of which are being submitted herewith.

The above-captioned patent application is directed to compositions and methods involving human neonatal or fetal hematopoietic stem cells and/or progenitor cells.

The following patents and publications are deemed to be the most pertinent to the claimed invention, although Applicants believe they neither anticipate the invention nor in any way render it obvious. The letters in brackets after each reference correspond to the references listed on attached revised form PTO-1449 entitled LIST OF REFERENCES CITED BY APPLICANTS.

A. Hematopoietic Stem and Progenitor Cells

1. Knudtzon, 1974, Blood 43(3):357-361 [AA]

2. Prindull et al., 1978, Acta Paediatr. Scand. 67:413-416 [AB]

3. Fauser and Messner, 1978, Blood 52(6): 1243-1248 [AC]

4. Hassan et al., 1979, Brit. J. Haematol. 41:477-484 [AD]

5. Vainchenker et al., 1979, Blood Cells 5:25-42 [AE]

6. Tchernia et al., 1981, J. Lab. Clin. Med. 97(3):322-331 [AF]

7. Nakahata and Ogawa, 1982, J. Clin. Invest. 70:1324-1328 [AG]

8. Linch et al., 1982, Blood 59(5):976-979 [AH]

9. Koizumi et al., 1982, Blood 60(4):1046-1049 [AI]

10. U.S. Patent No. 4,714,680, filed February 6, 1984 by Civin [AJ]

The 1974 reference by Knudtzon discloses in vitro colony-forming cells in human umbilical cord blood and in human adult peripheral blood. The in vitro colony-forming cells are reported to exist at higher concentrations in umbilical cord blood relative to those found in adult blood.

The 1978 reference by Prindull et al. describes the existence of in vitro colony-forming myelopoietic stem cells in human umbilical cord blood, at concentrations greater than that found in adult peripheral blood.

The 1978 reference by Fausner and Messner describes the presence of circulating hematopoietic progenitor cells in human cord blood, peripheral blood, and in bone marrow, and their ability to cause in vitro granuloerythrocytic colony formation.

The 1979 reference by Hassan describes erythroid colony formation in vitro by cells from human umbilical cord blood, from human fetal liver, and from adult peripheral blood. Increased numbers of erythroid progenitors, and differences in the characteristics of the erythroid colonies formed, were found associated with human cord blood or fetal liver relative to adult peripheral blood.

The 1979 reference by Vainchenker et al. describes the presence of megakaryocyte and burst erythroblast progenitors in human adult, fetal, and neonatal blood, and in human fetal liver, as assayed by colony formation in vitro.

The 1981 reference by Tchernia et al. describes the existence of erythroid progenitors in human umbilical cord blood, as assayed by colony formation in vitro. In the presence of erythropoietin, increased numbers of erythroid progenitors were detected in cord blood relative to adult blood.

The 1982 reference by Nakakata and Ogawa describes the presence of hematopoietic colony-forming cells in human umbilical cord blood, with the ability to generate progenitors for multipotential secondary colonies.

The 1982 reference by Linch et al. describes the presence of hematopoietic progenitor cells in human fetal blood, which cells are more sensitive to erythropoietin and colony-stimulating factor than are adult progenitor cells.

The 1982 reference by Koizumi et al. describes a comparative study of CFU-GM (colony-forming unit granulocyte/macrophage) from human umbilical cord blood and from human bone marrow, by the use of antibody to the Ia antigen plus complement. The results suggest some

differences in the characteristics of CFU-GM which express Ia antigen, from cord blood as compared to those in bone marrow.

U.S. Patent No. 4,714,680 discloses compositions comprising human hematopoietic stem cells from peripheral blood or bone marrow, that are substantially free of mature lymphoid and myeloid cells. Methods of obtaining such compositions based on anti-My-10 antibody binding are disclosed.

B. Bone Marrow Transplantation for Reconstitution of the Hematopoietic System

11. Thomas et al., Feb. 5, 1972, The Lancet, pp. 284-289 [AK]

12. Storb and Thomas, 1983, Immunol. Rev. 71:77-102 [AL]

13. O'Reilly et al., 1984, Sem. Hematol. 21(3):188-221 [AM]

14. Herzig, 1983, in Bone Marrow Transplantation, Weiner et al., eds., The Committee on Technical Workshops, American Association of Blood Banks, Arlington, Virginia [AN]

15. Dicke et al., 1984, Sem. Hematol. 21(2):109-122 [AO]

16. Spitzer et al., 1984, Cancer 54 (Sept. 15 Suppl.):1216-1225 [AP]

17. McGlave, 1985, in Recent Advances in Haematology, Hoffbrand, A.V., ed., Churchill Livingstone, London, pp. 171-197 [AQ]

18. U.S. Patent No. 4,721,096, filed April 3, 1987, by Naughton and Naughton [AR]

The 1972 reference by Thomas et al. describes the use of bone marrow transplantation for treatment of aplastic anemia.

The 1983 reference by Storb and Thomas reviews the use of allogeneic bone marrow transplantation for treatment of various diseases and disorders.

The 1984 reference by O'Reilly reviews the use of bone marrow transplantation for treatment of congenital disorders of the hematopoietic system and of certain congenital metabolic disorders.

The 1983 reference by Herzig reviews the use of autologous bone marrow transplantation, including methods of bone marrow procurement and cryopreservation. Attempts at using peripheral blood for hematopoietic reconstitution are also mentioned.

The 1984 reference by Dicke et al. reviews the use of autologous bone marrow transplantation for treatment of various malignancies.

The 1984 reference by Spitzer et al. reviews the use of autologous bone marrow transplantation and high-dose chemotherapy for treatment of various human tumors.

The 1985 reference by McGlave et al. reviews the therapeutic uses of allogeneic and autologous bone marrow transplantation.

U.S. Patent No. 4,721,096 describes methods for replicating bone marrow in vitro. Also disclosed are therapeutic methods of hematopoietic reconstitution comprising obtaining the bone marrow, replicating the bone marrow in vitro, and in some instances, cryopreserving the bone marrow.

C. The Use of Peripheral Blood for Hematopoietic Reconstitution

19. Nothdurft et al., 1977, Scand. J. Haematol. 19:470-481 [AS]

20. Hershko et al., 1979, The Lancet 1:945-947 [AT]

21. Sarpel et al., 1979, Exp. Hemat. 7(2):113-120 [AU]

22. Goldman et al., 1980, Brit. J. Haematol. 45:223-231 [AV]

23. Prummer et al., 1985, Exp. Hematol. 13:891-898 [AW]

24. Juttner et al., 1985, Brit. J. Haematol. 61:739-745 [AX]

25. Reiffers et al., 1986, Exp. Hematol. 14:312-315 [AY]

26. Tilly et al., July 19, 1986, The Lancet, pp. 154-155 [AZ]

27. Korbling et al., 1986, Blood 67(2):529-532 [BA]

28. Castaigne et al., 1986, Brit. J. Jaematol, 63(1):209-211 [BB]

29. Juttner et al., 1986, Exp. Hematol. 14(6):465 (Abstr. 312) [BC]

30. Stiff et al., 1986, Exp. Hematol. 14(6):465 (Abstr. 311) [BD]

31. To and Juttner, 1987, Brit. J. Haematol. 66:285-288 [BE]

The 1977 reference by Nothdurft describes the use of cryopreserved mononuclear cells derived from the peripheral blood in the autologous hematopoietic reconstitution of lethally irradiated dogs.

The 1979 reference by Hershko et al. describes the use of bone marrow transplantation to effect hematopoietic reconstitution in a patient with a type of aplastic anemia, and the failure to effect such reconstitution using peripheral blood mononuclear cells.

The 1979 reference by Sarpel et al. describes the autologous hematopoietic reconstitution of dogs through the use of cryopreserved peripheral blood mononuclear cells.

The 1980 reference by Goldman et al. describes the use of cryopreserved-thawed, autologous, peripheral blood nucleated cells for the hematopoietic reconstitution of patients with chronic granulocytic leukemia.

The 1985 reference by Prummer et al. describes the use of cryopreserved autologous peripheral blood leukocytes or bone marrow cells in the immune reconstitution of irradiated dogs.

The 1985 reference by Juttner et al. describes the use of peripheral blood cells, collected from patients in remission from acute lymphoblastic leukemia, for autologous hematopoietic reconstitution.

The 1986 reference by Reiffers et al. describes the use of cryopreserved peripheral blood cells, collected from a patient in remission from acute nonlymphocytic leukemia, for autologous hematopoietic reconstitution.

The 1986 reference by Tilly et al. describes the use of cryopreserved peripheral blood cells collected from acute leukemia patients for autologous hematopoietic reconstitution.

The 1986 reference by Korbling et al. describes the hematopoietic reconstitution of a patient with Burkitt's lymphoma through the use of autologous peripheral blood mononuclear cells collected from the patient and cryopreserved.

The 1986 reference by Castaigne et al. describes the hematopoietic reconstitution of a patient with promyelocytic leukemia, through the use of autologous peripheral blood mononuclear cells collected from the patient and cryopreserved.

The 1986 reference by Juttner et al. describes the use of cryopreserved peripheral blood stem cells collected from patients in remission from acute non-lymphoblastic leukemia, in the attempted autologous hematopoietic reconstitution of the patients.

The 1986 reference by Stiff describes the use of cryopreserved peripheral blood stem cells collected from patients with small cell lung cancer in the attempted autologous hematopoietic reconstitution of the patients.

The 1987 reference by To and Juttner describes the use of peripheral blood cells, collected from patients in early remission of various malignancies, for hematopoietic reconstitution, particularly for autologous reconstitution in the treatment of acute myeloid leukemia.

D. Other References Relating to Cell Transplantation

32. Tulunay et al., 1975, Proc. Natl. Acad. Sci. U.S.A. 72(10):4100-4104 [BF]

33. Touraine, 1980, Excerpta Medica Intl. 514:276-283 [BG]

34. Ochs et al., 1981, Pediatr. Res. 15(4 part 2):601 [BH]

35. Paige et al., 1981, J. Exp. Med. 153:154-165 [BI]

36. Hirokawa et al., 1982, Clin. Immunol. Immunopathol. 22:297-304 [BJ]

37. Vickery et al., 1983, J. Parasitol. 60(3):478-485 [BK]

38. Touraine, 1983, Birth Defects 19(3):139-142 [BL]

39. Good et al., 1983, Cellular Immunol. 82:36-54 [BM]

40. Cain et al., 1986, Transplantation 41(1):21-25 [BN]

The 1975 reference by Tulunay et al. describes the immunologic reconstitution of lethally irradiated mice through the use of syngeneic fetal liver cells or syngeneic newborn spleen cells or adult spleen cells. Immunologic reconstitution appeared to be affected by irradiation

dosage. Lethally irradiated mice did not survive after engraftment with newborn thymus cells or allogeneic newborn or adult spleen cells.

The 1980 reference by Touraine describes the use of combined fetal liver and thymus transplantation for the attempted immune reconstitution of four patients with severe combined immunodeficiency diseases.

The 1981 reference by Ochs et al. describes the use of red blood cells, peripheral blood mononuclear cells, fetal liver cells, or bone marrow cells for the attempted immune reconstitution and restoration of antibody response in patients with severe combined immunodeficiency associated with adenosine deaminase deficiency. Only the patient treated with bone marrow exhibited a normal antibody response.

The 1981 reference by Paige et al. describes a study of the B lymphocyte reconstitution potential and characteristics of B lymphocyte precursor cells in the mouse, by transplantation of adult bone marrow or fetal liver cells into mice.

The 1982 reference by Hirokawa et al. describes the use of young bone marrow cells, newborn thymus cells, or a combination thereof, for the attempted immune reconstitution of aging mice. The combination of bone marrow and thymus promoted an increase in specific immune response, to a level comparable to that of younger mice.

The 1983 reference by Vickery et al. describes the use of syngeneic thymus cell transplantation for immune reconstitution as assayed by resistance to the parasite Brugia pahangi.

The 1983 reference by Touraine describes the results of fetal thymus transplantation, fetal liver transplantation, or a combination thereof, for the treatment of patients with severe combined immunodeficiency.

The 1983 reference by Good et al. describes the use of bone marrow transplantation for treatment of various diseases. The use of fetal liver and newborn spleen transplantations is also discussed (pp. 44-45).

The 1986 reference by Cain et al. describes the occurrence of myasthenia gravis and polymyositis in a dog after immune reconstitution by transplantation of fetal liver cells.

E. Cryopreservation

41. Lovelock and Bishop, 1969, Nature 183:1394-1395 [BO]

42. Ashwood-Smith, 1961, Nature 190:1204-1205 [BP]

43. Rowe and Rinfret, 1962, Blood 20:636-637 [BQ]

44. Rowe and Fellig, 1962, Fed. Proc. 21:157 [BR]

45. Rowe, 1966, Cryobiology 3(1):12-18 [BS]

46. Lewis et al., 1967, Transfusion 7(1):17-32 [BT]

47. Zuckerman et al., 1968, J. Clin. Pathol. (London) 21(1):109-110 [BU]

48. Rapatz et al., 1968, Cryobiology 5(1):18-25 [BV]

49. Mazur, 1970, Science 168:939-949 [BW]

50. Robinson and Simpson, 1971, In Vitro 6(5):378 [BX]

51. Alink et al., 1976, Cryobiology 13:295-304 [BY]

52. Mazur, 1977, Cryobiology 14:251-272 [BZ]

53. Kemp et al., 1978, Transplantation 26(4):260-264 [CA]

54. Fabian et al., 1982, Exp. Hematol. 10(1):119-122 [CB]

55. Hull, 1983, in American Type Culture Collection, Quarterly Newsletter 3(4):1 [CC]

56. Rowe and Lenny, 1983, Cryobiology 20:717 (Abstr. 70) [CD]

57. Stiff et al., 1983, Cryobiology 20:17-24 [CE]

58. Gorin, 1986, Clinics in Haematology 15(1):19-48 [CF]

The 1959 reference by Lovelock and Bishop describes the protective effect of dimethyl sulfoxide against damage to red blood cells and spermatozoa caused by freezing.

The 1961 reference by Ashwood-Smith describes the protective effect of dimethyl sulfoxide to prevent damage to mouse bone marrow cells cryopreserved at -79°C for one month, and the ability of such cells to effect hematopoietic reconstitution in lethally irradiated mice.

The 1962 reference by Rowe and Rinfret describes optimal cooling rates for preserving viability of cryopreserved bone marow cells.

The 1962 reference by Rowe and Fellig describes the results of a study on the viability of bone marrow cells cryopreserved in the presence of various protective agents. Dimethyl sulfoxide and mannitol were found to preserve the viability of the frozen cells as measured by both staining and metabolic activity criteria.

The 1966 reference by Rowe describes various cryoprotective agents and the efficiency and mechanisms of their protective actions, with regard in part to the viability of cryopreserved bone marrow and red blood cells.

The 1967 reference by Lewis et al. describes a study of the effect of various cooling regimens upon the ability of cryopreserved bone marrow cells to effect hematopoietic reconstitution of lethally irradiated mice.

The 1968 reference by Zuckerman et al. describes the cryopreservation and thawing of viable human fetal liver cells.

The 1968 reference by Rapatz et al. describes a study on the viability of erythrocytes in whole blood, cryopreserved at various cooling rates, with or without cryoprotective agents. The mode of protective action of both dextrose and glycerol was shown to be dependent upon the cooling rate.

The 1970 reference by Mazur reviews the physical-chemical events during cryopreservation and factors affecting the viability of cryopreserved cells, as well as the effects and action of various cryopreservatives. The effect of cooling velocity on cells such as bone marrow stem cells and red blood cells is disclosed.

The 1971 reference by Robinson and Simpson describes a study of the viability of fibroblast-like cells and of fetal myocardial cells upon cryopresrvation in the presence and absence of dimethyl sulfoxide and glycerol.

The 1976 reference by Alink et al. describes a study of the viability of neonatal rat heart cells upon cryopreservation using various cooling rates and dimethyl sulfoxide concentrations. Five °C per minute was found to be an optimal cooling rate for all DMSO concentrations. Optimal cooling rates for other cell types, including marrow stem cells and red blood cells, are disclosed.

The 1977 reference by Mazur describes the physical events which occur during cell freezing, the effect of cooling rate on survival of cells such as red blood cells, and the effect of cryoprotective agents such as glycerol and dimethyl sulfoxide. The survival of cryopreserved mouse bone marrow stem cells and human red cells in various concentrations of glycerol are disclosed.

The 1978 reference by Kemp et al. describes the transplantation of cryopreserved and thawed fetal rat pancreases into syngeneic induced-diabetic adult rats, and the resultant reversal of diabetes.

The 1982 reference by Fabian et al. describes a study of the ability of human hematopoietic bone marrow stem cells to withstand cryopreservation and thawing. Human bone marrow stem cells were shown capable of withstanding such procedures without significant cell death, as demonstrated by the ability to form almost the same number of mixed myeloid-erythroid colonies in vitro after freezing.

The 1983 reference by Hull describes the successful recovery of cells, including human bone marrow cells, after long-term storage in liquid nitrogen, and discloses the freezing methods which were used.

The 1983 reference by Rowe and Lenny describes a study of the viability of red blood cells upon cryopreservation using two different freezing techniques.

The 1983 reference by Stiff et al. describes a study of bone marrow cell viability upon cryopreservation in a mixture of DMSO and hydroxyethyl starch (HES), compared to the use of DMSO alone. Use of the mixture yielded greater cell viability, as assayed by trypan blue exclusion and production of CFU-C in vitro, and less cell clumping upon thawing.

The 1986 reference by Gorin reviews techniques for the procurement, manipulation, cryopreservation, thawing and evaluation of hematopoietic stem cells from bone marrow or adult peripheral blood.

F. Gene Therapy

59. Miller et al., 1984, Science 255:630 [CG]

60. Cline, 1985, Pharmac. Ther. 29:69-92 [CH]

61. Spalding, July 29, 1987, Chemical Week, p. 27 [CI]

The 1984 reference by Miller et al. describes the expression in murine hematopoietic tissue of human hypoxanthine phosphoribosyl transferase (HPRT), achieved by the transfer of HPRT into mouse bone marrow cells by use of a retrovirus vector and then transplantation of the recombinant bone marrow cells into mice.

The 1985 reference by Cline reviews techniques for gene transfer useful in the area of gene therapy. Chromosome transfer, physical, and viral vector methods are discussed. Therapeutic applications are also described.

The 1987 reference by Spalding discloses the idea of inserting antisense genes against the AIDS virus into bone marrow cells, for use in autologous bone marrow transplantation for treatment of AIDS.

Identification of the above-listed references is not to be construed an admission of Applicants or Attorneys for applicants that such references are available as "prior art" against the subject application. Consequently, Applicants respectfully decline to use form PTO-1449, since this form identifies all of the references cited therein as "Prior Art." As an alternative, Applicants submit herewith

several pages of a "revised form PTO Form 1449" entitled "List of References cited" instead of "List of Prior Art Cited."

Applicants respectfully request that the Examiner review the foregoing references and that the references be made of record in the file history of the application.

Respectfully submitted,

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